HESI at THIRTY

The past, present and future of collaborative science

30 THIRTY YEARS HESI

Science for a Safer, More Sustainable World

Improving Health Outcomes for High Risk Neonates via Safer Therapeutic Intervention

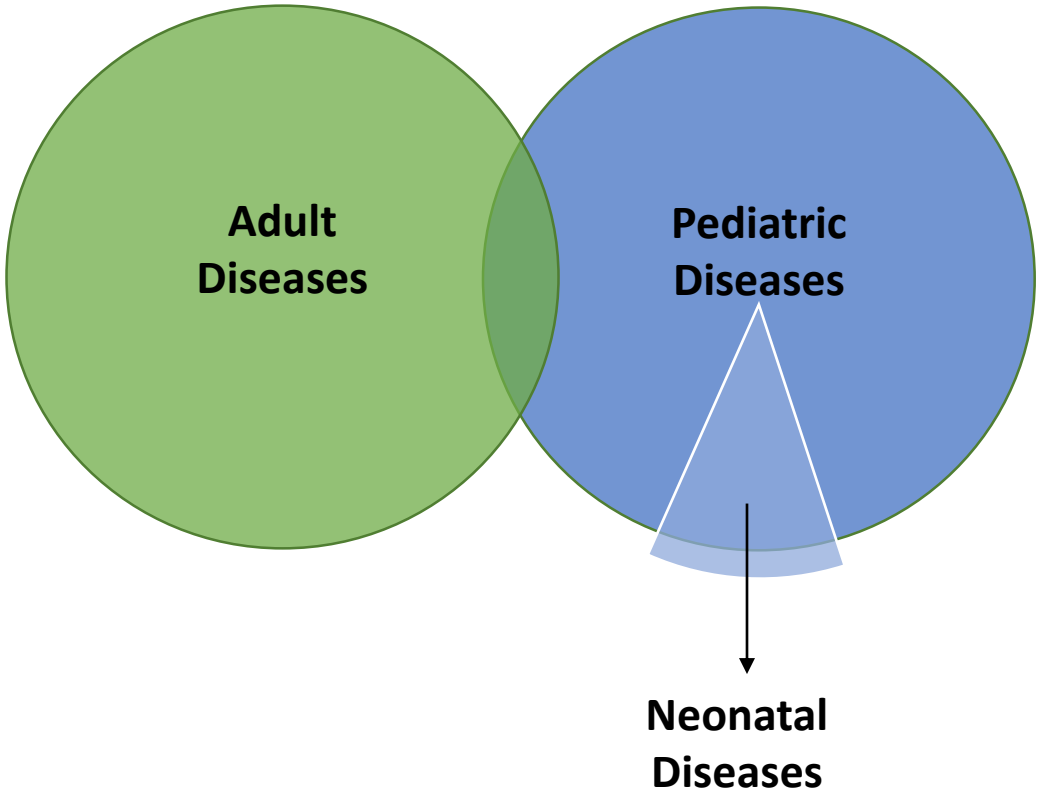
Kary E. Thompson, Bristol-Myers Squibb
On behalf of the DART Technical Committee

The Problem

- 90% NICU drugs are used off-label
- Often treated with multiple medicines at the same time
- Adverse drug effects (ADEs) 3x more likely
- NICU patients have the highest medical errors and ADE rates (sparse data on correct use of medicines)
- Very few therapies are being developed for neonates
- Prematurity rates:
  - EU: 5-10%
  - USA: 12% (worst of any developed country; 131st in the world)

This Photo by Unknown Author is licensed under CC BY-NC-ND

Therapeutic Orphans:
The Drug Development Disconnect



- **Neonatal studies are regarded as not needed**
- **Disease does not occur in newborns (but does in 1 yr olds)**
- **Are neonatal studies too difficult?**
  - Ethical, emotional concerns
  - Knowledge gaps in nonclinical models of neonatal diseases
  - Endpoints do not apply or cannot be measured in newborns
  - PK difficult to measure in newborns, need new formulations
  - Study designs for pediatrics do not fit newborns e.g., smaller # patient population
  - Should limit studies in newborns based on AE in adults, assuming they occur in neonates (e.g., QTc?)

Addressing the Disconnect: Ongoing Efforts

S11 Guideline

Provides direction on the **nonclinical safety studies important to support a pediatric development program**. It will recommend **standards** for the conditions under which **nonclinical juvenile animal testing** is considered informative and necessary to support pediatric clinical trials and provide **guidance on the design of the studies**.(Draft Guideline developed Sept 2018.)

Regulatory requirement for a Pediatric Study Plan (FDA) and Pediatric Investigational Plan (EMA) needed before submission of New Drug Application or Marketing Authorization Application.

- Food and Drug Administration Safety and Innovation Act (FDASIA) 2012
- European Commission Pediatric Regulation No 1901/2006

PRECLINICAL → **CLINICAL**

DART Technical Committee

- Emerging Issues proposal submitted in 2014
  - **Nonclinical Efficacy and Safety Studies to Support Neonatal Therapeutics**
- Adopted by DART Committee in 2015
  - Extensive nonclinical expertise within the committee
  - Leveraged connections to bring in external expertise

International Neonatal Consortium

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.

NEONATAL LUNG INJURY AND CIRCULATORY FAILURE	NEONATAL GASTROINTESTINAL INJURY
PERINATAL/NEONATAL INFECTIONS	NEONATAL BRAIN INJURY
NEONATAL ABSTINENCE SYNDROME (NAS)	DRUGS TO PREVENT PRETERM LABOR
RETINOPATHY OF PREMATURITY (ROP)	

DART Technical Committee:
Nonclinical Studies to Bridge the Data Gaps

- ✓ **Identify relevant animal models for developmental stage or disease condition of preemie/neonate**
  - What models are available?
  - What aspect of the condition do they model effectively?
  - What is the limitation of the model?

- ✓ **Provide knowledge of the pharmaco-dynamics during development**

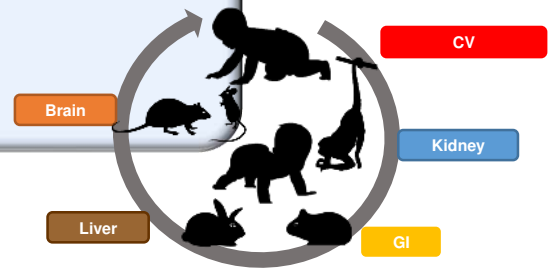
- ✓ **Assess long term effects of acute & chronic treatment on development & outcome**

- Identify relevant models of neonatal disease and explore therapeutic options and strategies

SURVEY OF EXISITING MODELS

NEONATE PHYSIOLOGY

- Increase understanding of comparative physiology development between neonates and nonclinical animal species

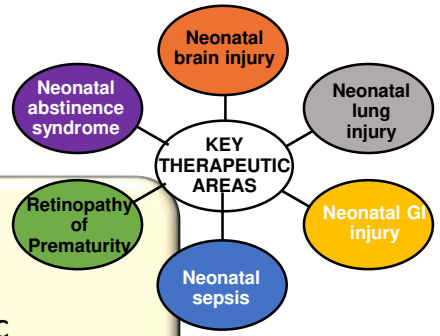


STARTING DOSE

- Demonstrate where nonclinical models can inform dose selection in neonates through case studies

RESEARCH FRAMEWORK

Frame the basic principles for evaluating new animal models to address key therapeutic questions in neonates

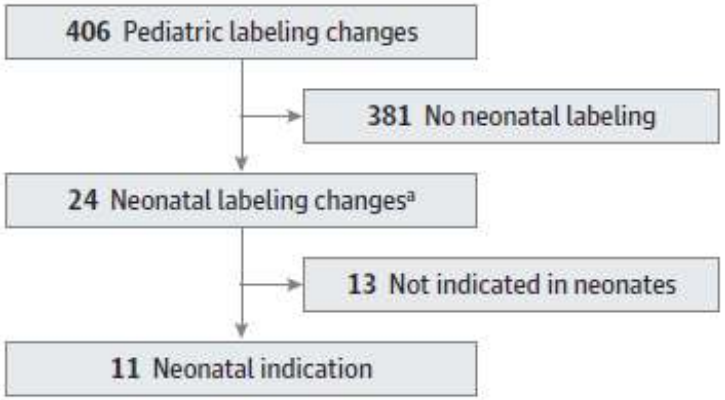


Health and Environmental Sciences Institute
Science for a Healthier World

This Photos by Unknown Author is licensed under CC BY

Neonatal Drugs:
A Snapshot of the Regulatory Landscape

Figure. Neonatal Labeling Changes Under Legislation From 1997 to 2010 and Exposure of Neonates to Drugs With a Neonatal Indication



[a]There are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.

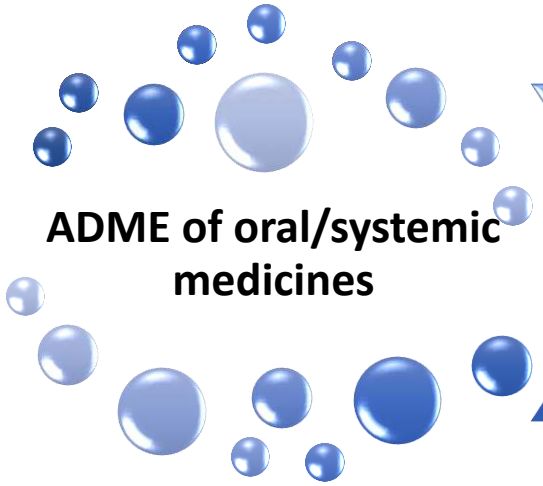
Laughon MM, Avant D, Tripathi N et al. 2014. Drug labeling and exposure in neoates. *JAMA Pediatr*.168:130-136.

- 28 drugs studied in neonates (US)

- 1 in 4 PIPS specifically mention neonatal development (Europe)
- Inclusion of neonates increased from PIPs:
  - 15% - 25% in 2008
  - 24% - 32% in 2011

Neonate Physiology

Increasing the understanding of comparative physiological development between neonates and nonclinical animal species



Age of patient or animal

Selection of animal model

- Species
- Maturational age changes (physiology)
- Ontogeny profiles of enzyme, transporters, nuclear receptors

Drug efficacy and toxicity

Neonate Physiology:

Increasing the understanding of comparative physiological development between neonates and nonclinical animal species

Overview

Completed

De Schapedrijver et al. 2019. Drug Metab Dispos.

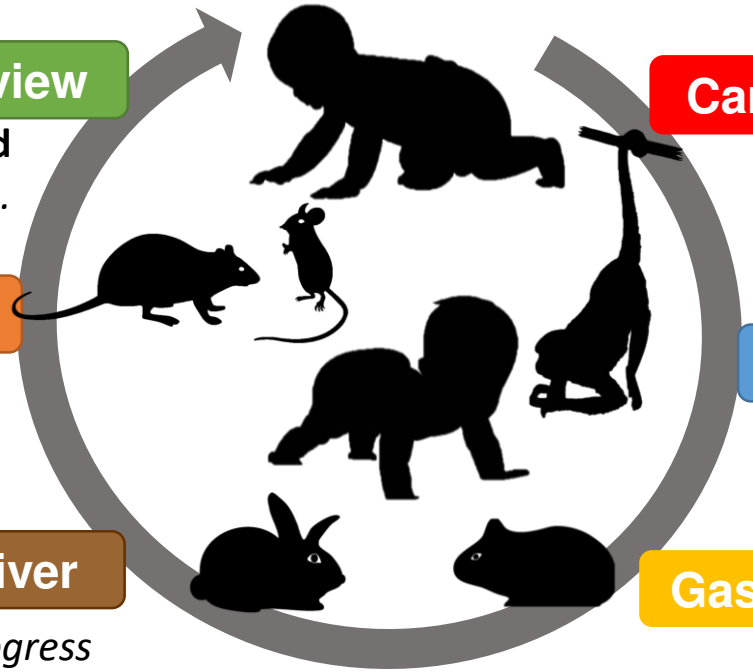
Brain

Will be integrated to second phase (case studies)

Liver

In progress

Anticipated completion in Summer 2019



Cardiovascular

Completed

Hausner et al. 2019. Drug Metab Dispos.

Kidney

In internal & HESI reviews

Gastrointestinal

Completed;

Kluever et al. 2019. Drug Metab Dispos.

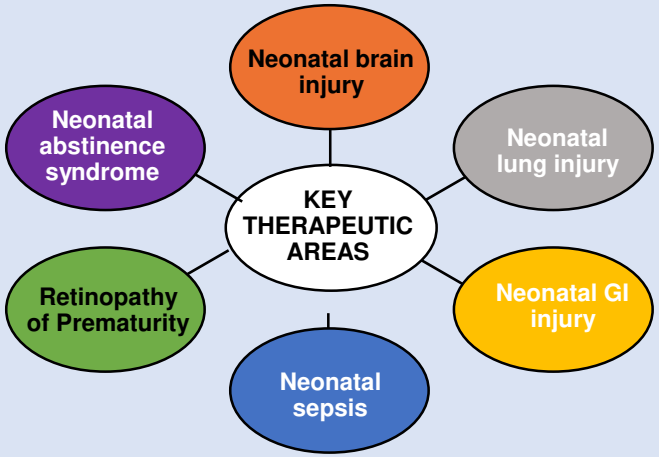
Research Framework:

Framing the basic principles for evaluating existing and developing new models to address key therapeutic questions in neonates

What are the **basic principles for the construction of an animal model** to study questions in neonates?

How can **we help guide researchers to work with existing nonclinical models or establish new models** to further research these diseases and support clinical development and success of future therapies?

1. Performed literature searches to identify available nonclinical models for 6 diseases affecting neonates:



- INC clinicians identified the most common NICU conditions (premature birth not within current scope of work)
- Research into nonclinical models to complement INC work on clinical aspects

2. Completed summaries of available nonclinical models for each disease

- **How well does the model capture the key clinical hallmarks of each disease?**
- **What is the species and model relevance to humans?**
- **What is the model application: mechanism, efficacy, and/or safety?**

3. Make integrated assessment:

- Are there common elements among the neonatal disease models or specific elements for each disease state?
- Summarize the gaps in information that animal models cannot address
- Provide recommendations for researchers working in these areas

4. Inform and promote future research!

Research Framework:

Preliminary Conclusions for Integrated Assessment

Many of the **evaluated models are geared towards investigating mechanisms and/or efficacy.**

- Much less focus on safety

Various **species** used with clear **preference** for **rodents**.

- Sheep, pig and primates appear to be useful for some of the neonatal diseases but not widely used

In many cases it seems that treatments that are effective in animal models **do not translate to efficacy in the clinic**

- Reflection of inherent species and developmental differences
- Lack of standardized protocols (methodological concerns)
- Lack of understanding of mechanisms underlying the disease

No single animal model completely covers the complexity of the human condition.

- May need a combination of models to cover all aspects of a particular disease

Points to consider when developing a new disease model:

- Physiological similarities/differences between species
- Understanding strengths and limitations
- Model must effectively capture the precipitating human event / early aspects of the disease
- Consider the goal of the research
- Need to pick an age when the target organ in the animal model is at the same developmental stage as in the neonate

Starting Dose:

Demonstrate where nonclinical models can inform dose selection in neonates through case studies

- White paper, building on recent INC clinical pharmacology paper, to address levering all sources of info to optimize dose selection for neonates, taking into account prenatal and postnatal physiology
  - Adult studies
  - Pediatric studies
  - Non-clinical and juvenile studies
  - *In vitro* studies
  - *In silico* models

Overview of Case Studies

Key Components

Disease status

- Is it related to children or adults?

Clinical ADME characteristics

- Disease mechanism
- Significant ADME considerations?
- Additional safety info needed?

Target dose animal model information needed

- Adult animal model?
- Juvenile animal model?
- Maturational toxicity known?

***in vitro* model info needed**

- Reflective of neonatal ADME
- Reflective of neonatal state?

Clinical data information available

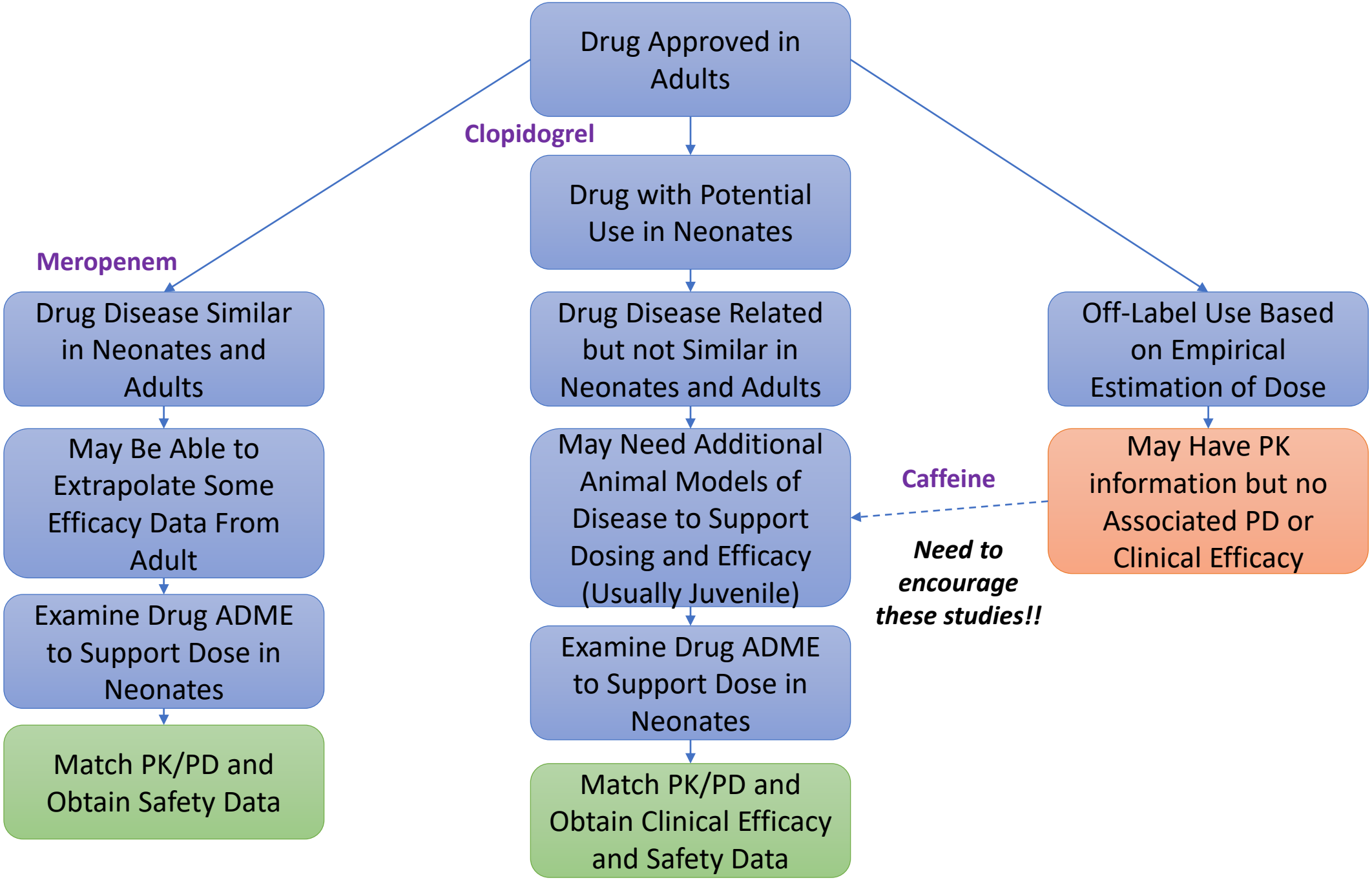
- Adult data available?
- Pediatric data available?
- Safety and PK/PD info in neonates available?

Known trial design considerations

- Is the info in labels?

Final Case Studies:

- Meropenum
- Clopidogrel
- Caffeine
- Synthroid
- Surfactant

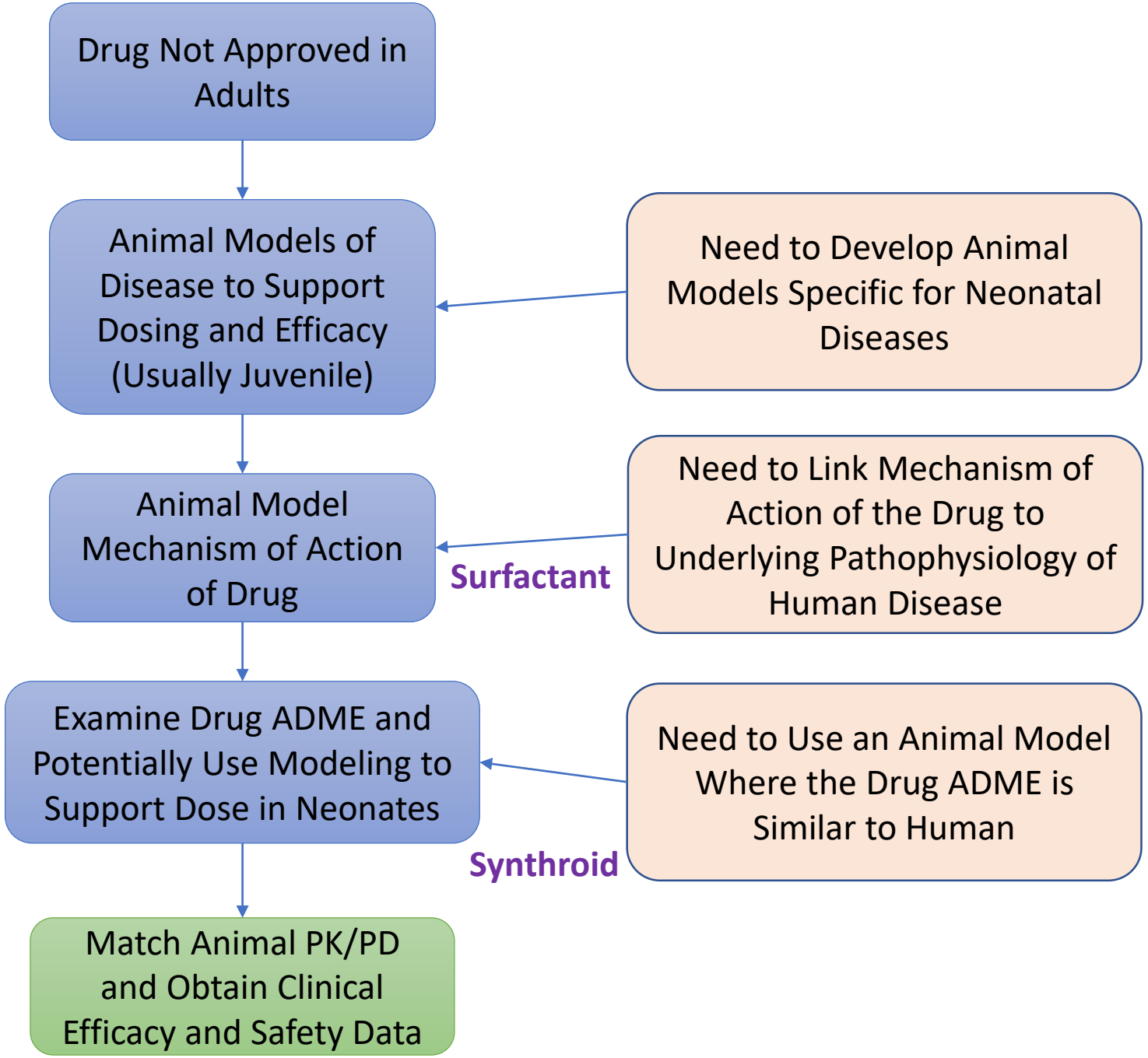


30 THIRTY YEARS HESI Science for a Healthier World

Clinical Development Plan

Phase 1 Trials in Healthy Volunteers Not Ethical in Pediatric Patients and May Not be Possible in Adults Depending on the Route of Administration and Potential Toxicity

Phase 2 Trials for Proof of Concept and Safety May Need to be Done in Neonates with the Disease or Condition



30 THIRTY YEARS HESI Science for a Healthier World

Key Takeaways

- Dosing strategies are difficult for neonates
- Juvenile animal models can be used to:
  - Understand mechanism of action of the drug and ontogeny of organ systems to predict on/off-target effects
    - Role of metabolizing enzyme systems
  - Models of clinical disease
    - Dose ranging studies
    - Proof of concept studies
    - Safety studies
  - PBPK modeling
- Need to develop more *in vitro*, *in vivo*, and *in silico* models to help optimize dosing strategies for first in human trials in neonates

Next Steps

This Photo by Unknown Author is licensed under CC BY

- Large compendium of information published and in-press:
  - Symposia
  - CE or other educational courses
- Primary audiences
  - Preclinical
  - Clinical
    - Int'l Neonatal Consortia
    - American Academy of Pediatrics
- Other next steps will also be informed by ICH S11 conversations

ICH harmonisation for better health

FDA

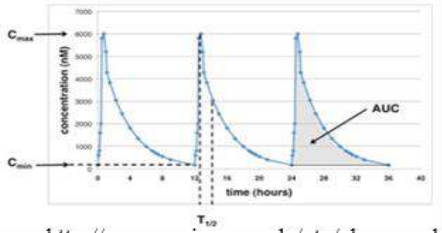
EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

INC CRITICAL PATH INSTITUTE
International Neonatal Consortium

Right Drug

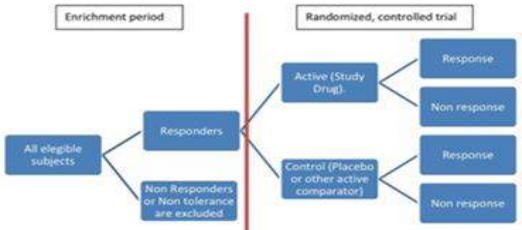
Right Population

Right Dose

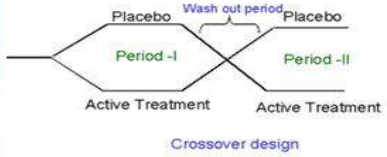


http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm

Right Trial Design

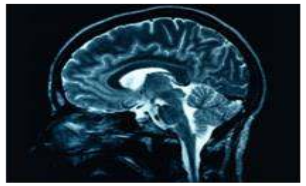


http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html



http://accp1.org/pharmacometrics/theory.htm

Right Endpoints



Thanks to …

Overall Project Leads:	Survey	Physiology	Research Framework	Dose
Karen Davis-Bruno (US FDA) Luc de Schaepdrijver (Janssen)	Vijay Umaliya (Janssen) Susan Laffan (GSK)	Luc de Schaepdrijver (Janssen) Pieter Annaert (U Leuven)	Sarah Campion (Pfizer)	Suzie McCune (US FDA)

INDUSTRY

- AbbVie, Inc.
- AstraZeneca AB
- Biogen Inc.
- Boehringer-Ingelheim GmbH
- Celgene Corporation
- Charles River Laboratories
- Chiesi Pharmaceuticals*
- Covance, Inc.
- Eli Lilly and Company
- Genentech
- GlaxoSmithKline
- Hoffmann-La Roche
- Janssen Pharmaceuticals
- Merck & Co. Inc.
- Pfizer, Inc.
- Sanofi
- Takeda Pharmaceutical Company Limited

GOVERNMENT/REGULATORY

- Federal Institute for Medicines and Health Products (Belgium)
- Health Canada
- Karolinska Institute*
- Medicines and Healthcare Products Regulatory Agency (UK)
- Medicines Evaluation Board (The Netherlands)
- National Agency of Medicine and Health Products Safety (ANSM, France)*
- National Institute for Public Health and the Environment (RIVM, The Netherlands)
- National Institute of Environmental Health Sciences
- National Toxicology Program
- US Food and Drug Administration

ACADEMIC

- Erasmus University*
- Ghent University*
- McMaster University
- Radbound University, Nijmegen Medical Centre*
- University of Leuven*

CONSULTING/RESEARCH

- Aclario Pharmaceutical Developmental Group, Inc.
- Critical Path Institute
- Exponent, Inc.

**new organizations to HESI DART*